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# Issues in the design of multisite clinical trials of psychotherapy: VA Cooperative Study No. 494 as an example

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**Abstract**

This article describes issues in the design of an ongoing multisite randomized clinical trial of psychotherapy for treating posttraumatic stress disorder (PTSD) in female veterans and active duty personnel. Research aimed at testing treatments for PTSD in women who have served in the military is especially important due to the high prevalence of PTSD in this population. VA Cooperative Study 494 was designed to enroll 384 participants across 12 sites. Participants are randomly assigned to receive 10 weekly sessions of individual psychotherapy: Prolonged Exposure, a specific cognitive–behavioral therapy protocol for PTSD, or present-centered therapy, a comparison treatment that addresses current interpersonal problems but avoids a trauma focus. PTSD is the primary outcome. Additional outcomes are comorbid problems such as depression and anxiety; psychosocial function and quality of life; physical health status; satisfaction with treatment; and service utilization. Follow-up assessments are conducted at the end of treatment and then 3 and 6 months after treatment. Both treatments are delivered according to a manual. Videotapes of therapy sessions are viewed by experts who provide feedback to therapists throughout the trial to ensure adherence to the treatment manual. Discussion includes issues encountered in multisite psychotherapy trials along with the rationale for our decisions about how we addressed these issues in CSP #494.


*Keywords:* Psychotherapy research; Posttraumatic stress disorder (PTSD); Cognitive–behavioral therapy; Women; Military veterans

Exposure to events such as sexual assault, combat, and accidents can have profound effects on a person's well-being. One of the most significant consequences is the development of posttraumatic stress disorder (PTSD). The lifetime prevalence of PTSD among adults in the US is 5% in men and 10% in women [1]. Evidence from large

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epidemiological studies indicates that lifetime prevalence is even higher among women who have served in the military, e.g., 17% among active duty female Navy and Marine Corps personnel [2], 26% among female Vietnam veterans [3]. PTSD is associated with a range of functional impairments, comorbid psychiatric disorders, and economic costs [e.g., 1,3–5]. For example, women with PTSD are 2.5–4.5 times as likely as women without PTSD to have a history of substance abuse or dependence [1].

Given the common occurrence of PTSD, and the human and economic costs associated with it, there is a great need to develop effective treatments for this disorder. Research aimed at testing treatments for PTSD in women who have served in the military is especially important due to the high prevalence of PTSD in this population. However, no randomized clinical trials (RCTs) of PTSD treatment targeting active duty or veteran women have been conducted.

In 1996, the VA Cooperative Studies Program (CSP) funded CSP #420, a large, multisite trial of group psychotherapy for PTSD. In that study, 360 male Vietnam veterans were randomly assigned to trauma-focused or present-centered group psychotherapy across 10 sites. Schnurr and colleagues [6] previously described the design and method of that study, which involved unique issues related to the delivery of psychotherapy in a group format and maintaining quality control of treatment delivery given the large number of sites.

In this article we discuss CSP #494, a randomized clinical trial of Prolonged Exposure (PE) [7,8] for treating PTSD in female veterans and active duty personnel. PE is an individual cognitive–behavioral therapy for PTSD in which a patient is asked to repeatedly recount the traumatic event until the patient's emotional response decreases and to gradually confront safe but fear evoking trauma reminders [9]. The study is a two-arm, parallel design comparison of PE versus a present-centered therapy (PCT) that controls for the common benefits of psychotherapy. We hypothesize that PE will be more effective than PCT for treating symptoms of PTSD and other comorbid problems.

The apparent simplicity of the design of an RCT, typically a two-group comparison, obscures the complexities of the methods needed to ensure its validity and successful completion. Multisite research, which is an important step in the evaluation of a treatment because it facilitates the use of large samples and enhances generalizability, adds additional complexities due to the need to ensure standardization and supervision of the protocol across sites. Psychotherapy research adds further complexities of design (e.g., how to choose and implement an appropriate comparison therapy) and method (e.g., how to best ensure adherence to treatment manuals). Below we use CSP #494 as an example to discuss issues encountered in multisite psychotherapy trials and provide the rationale for our decisions about how we addressed these issues in CSP #494. First we summarize the study's design and method.

## 1. Design and method of CSP #494

### *1.1. Participants*

Each of 12 sites is projected to enroll 32 participants over 24 months of active recruitment (total $N=384$). Participants must be female veterans or active duty personnel with a current diagnosis of PTSD due to any type of trauma, with diagnosis determined by meeting DSM-IV diagnostic criteria [10] and a score of 45 or greater on the Clinician Administered PTSD Scale (CAPS) [11]. They must: have experienced trauma no less than 3 months before entering the trial; have at least one clear memory of the trauma that caused their PTSD (sufficient for constructing a scene to be used in PE); not receive other psychotherapy for PTSD while receiving study treatment; and, if on psychoactive medication, have been on a stable regimen for at least 2 months.

Participants are excluded for any of the following reasons: current substance dependence; prior substance dependence that has not been in remission at least 3 months; any current psychotic symptoms; current Mania or Bipolar Disorder; prominent current suicidal or homicidal ideation; any severe cognitive impairment or history of cognitive disorder; current involvement in a violent relationship; or self-mutilation within the past 6 months. Potential participants who were excluded due to reversible criteria were given the option to be considered for inclusion if they met all criteria at a later date.

Two considerations guided the choice of inclusion/exclusion criteria: generalizability and patient safety. We included women with current substance abuse and most other psychiatric disorders to ensure that participants were as similar as possible to the general population of women with PTSD, who have numerous comorbid difficulties

[1,5,12]. However, women were excluded if they had comorbidities that could compromise safety during PTSD treatment. For example, we excluded women who engaged in self-injurious behavior within the prior 6 months, which was seen as an indication of adequate control over the self-injurious behavior. When a patient is exhibiting behavior that is potentially and imminently dangerous to self or others, good clinical practice dictates that treatment intervention should first be directed at amelioration of the dangerous behavior. Although our exclusion criteria thus may limit the generalizability of findings to the entire population of women with PTSD, the criteria permit generalization to women with PTSD who are appropriate candidates for PE, PCT, or other similar types of psychotherapy.

### *1.2. Assessment*

Our aim is to measure treatment outcome comprehensively but efficiently in order to minimize participant burden and cost. One consideration in the selection of each measure was the comparability it would facilitate to other relevant samples. Five domains are assessed: (a) PTSD and comorbid problems such as depression and anxiety; (b) psychosocial function and quality of life; (c) physical health status; (d) satisfaction with treatment; and (e) utilization of physical and mental health services. A masters- or doctoral-level Assessment Technician who is blind to a participant's treatment condition conducts all assessments.

The schedule of assessments is shown in Table 1. Most outcomes were measured at baseline, post-treatment, and 3 and 6 months post-treatment. Although some PTSD treatment studies have followed participants longer than 6 months [e.g., 8,23,24], this endpoint was chosen to balance the need to evaluate the durability of effects versus the cost of extending follow-up.

The primary outcome is PTSD symptom severity, as measured by the Clinician Administered PTSD Scale [11]. Additional measures of PTSD are the PTSD Checklist [13] and the percentage of participants who show clinically significant improvement on the CAPS, defined as a decrease of 10 or more points. Secondary outcomes are depressive symptoms, as measured by the Beck Depression Inventory [14], and anxiety symptoms, as measured by the State-Trait Anxiety Inventory [15]. Exploratory outcomes are drug and alcohol use, as measured by Addiction Severity Index subscales [16]; SF-36 Health Status Questionnaire [17]; Trauma Symptom Inventory subscales [18]; Quality of Life Inventory [19]; satisfaction with treatment [20]; and service utilization [21]. The Structured Clinical Interview for

Table 1
Schedule of assessment procedures by domain

| Domain | Screening | 2,4,6,8,10 | Weeks treatment | Post- | |
|---|---|---|---|---|---|
| | | | | 3-months | 6-months |
| PTSD/psychological | | | | | |
| CAPS | X | | X | X | X |
| PTSD checklist | X | X | X | X | X |
| Beck Depression Inventory | X | | X | X | X |
| Spielberger Anxiety Inventory | X | | X | X | X |
| SF-36 (subscale) | X | | X | X | X |
| ASI (subscales) | X | | X | X | X |
| TSI (subscales) | X | | X | X | X |
| SCID X | | | | | |
| Military stress exposure | X | | | | |
| Psychosocial function | | | | | |
| SF-36 (subscales) | X | | X | X | X |
| QOLI | X | | X | X | X |
| Physical health | | | | | |
| SF-36 (subscales) | X | | X | X | X |
| Satisfaction with treatment | | | X | | |
| Utilization | | | | | |
| Brief utilization interview | X | | X | X | X |
| Total estimated hours | 4–5 | 5 min | 2.5 | 2.5 | 2.5 |

CAPS=Clinician-Administered PTSD Scale; SF-36=Short Form 36; ASI=Addiction Severity Index; TSI=Traumatic Stress Inventory; SCID=-Structured Clinical Interview for DSM-IV; QOLI=Quality of Life Inventory.

DSM-IV (SCID) [22] is used during screening to establish exclusion diagnoses. The Global Assessment of Functioning Scale from the SCID also will provide an overall measure of functioning at baseline. The Military Stress Inventory for Women [12] provides a continuous measure of the amount of traumatic and nontraumatic stress experienced during military service.

All SCID and CAPS interviews are audiotaped. Twenty-five percent of the SCIDs and 12.5% of the CAPS are randomly selected in an ongoing way in order to monitor reliability. An Assessment Adherence Monitor, a doctoral-level clinical psychologist at the study's coordinating site, conducts reliability assessments. In order to maintain reliability, the Monitor provides feedback to Assessment Technicians during biweekly individual telephone supervision sessions and monthly group conference calls that continue throughout the study period.

### *1.3. Enrollment*

Enrollment involves a three-stage process that was used successfully in CSP #420 [6,23] to maximize screening efficiency and minimize dropout. All participants enter the study through a clinician at the participating site. Women who are not currently receiving treatment at the site must first undergo an intake at the site's mental health program. This strategy is intended to enhance referral appropriateness and provide continuity of care for women who are not enrolled in the study, discontinue treatment, or need additional treatment during the study.

In the first phase of screening, the Assessment Technician consults the referral source to establish a provisional PTSD diagnosis and determine whether the potential participant is likely to meet the other inclusion and exclusion criteria. In the second phase, the Assessment Technician meets with the potential participant and ascertains her willingness to adhere to study conditions. The Technician reviews the Informed Consent form and provides a copy of the form for the woman to take home. The Technician also asks about the woman's ongoing mental health treatment. Any necessary contacts with providers (to ensure their understanding of the study protocol regarding the provision of non-study treatment) are made prior to the third phase of screening. In the third phase, a potential participant gives signed consent and the Assessment Technician then assesses PTSD and other psychiatric diagnoses. If the potential participant meets the diagnostic eligibility criteria, the Technician completes the baseline assessments.

### *1.4. Treatment*

Eligible participants are randomly assigned to either PE or PCT following the baseline assessment. Efforts are made to limit the interval between randomization and treatment to 2 weeks or less. If the interval extends beyond a month, the CAPS is readministered so that baseline measurement occurs sufficiently close to the initiation of treatment.

#### *1.4.1. Prolonged exposure*

PE is delivered according to a manual tested in single-site trials with civilian men and women [7,8,24]. It consists of 10 weekly 90-min treatment sessions. Procedures include: education about common reactions to trauma; breathing retraining; prolonged (repeated) recounting (imaginal exposure) of the trauma memories during sessions; repeated in vivo exposure to safe situations the patient is avoiding because of trauma-related fear as between-session homework; and discussion of thoughts and feelings related to exposure exercises. Each session begins with a review of the homework assignment and presentation of the agenda for that session, and ends with the assignment of homework. Sessions 1 and 2 are devoted to information gathering, education about common reactions to trauma, developing a hierarchy of feared situations for in vivo exposure exercises, and fostering therapeutic alliance. Sessions 3 to 10 consist of homework review, recounting the traumatic memory and processing of the experience, discussion of in vivo exposures, and homework assignments.

#### *1.4.2. Present-centered therapy*

PCT is delivered according to a manual based on a supportive counseling model developed by Foa et al. [7]. For this study, the approach was modified to increase emphasis on the connections between current problems and PTSD symptoms. It is called present-centered therapy to emphasize the focus on the individual's current life and to conceptualize the problems addressed as manifestations of PTSD that in some cases may have been present for

long periods of time. The aim of these modifications is to provide a credible therapeutic alternative that clinicians can support while still allowing PCT to serve as a control for nonspecific therapeutic factors. The treatment follows the same format as PE, i.e., 10 weekly 90-min sessions. The therapist helps the patient identify daily stresses and discusses them in a supportive non-directive mode. No instructions for exposure are included. If the patient brings up trauma-related issues, the therapist gently redirects her to discuss other material.

*1.4.3. Additional treatment*

Participants may receive additional types of treatment during the 10 weeks of study therapy. They are allowed to stay on medication, attend self-help groups, and receive treatment for mental health problems other than PTSD. Participants who have a therapist outside of the study are allowed to see the therapist for brief supportive sessions if necessary. These check-ins may not be more frequent than once every 2 weeks and not exceed 10–15 min. Participants may consult about special problems that they experience but may not discuss trauma or study treatment.

In addition, participants who develop problems requiring additional inpatient or outpatient treatment are allowed to receive the additional treatment. They may stay enrolled in study treatment if this would be clinically appropriate, as determined by the therapist, Site Participating Investigator, and Master Therapist for the treatment to which the participant has been assigned. The amount and type of additional treatment is monitored at posttreatment using an interview measure derived from the Longitudinal Interval Follow-up Evaluation interview [21]. After completing study treatment, participants may seek additional treatment outside the study. Use of these treatments is recorded in the assessments at 3- and 6-month follow-up.

*1.4.4. Discontinuation*

Treatment is discontinued for participants who: become actively suicidal or homicidal; engage in an uncontrolled episode of alcohol or drug abuse that requires immediate treatment; require inpatient psychiatric treatment and further study treatment is determined to be clinically inappropriate; resume or initiate a relationship in which they are being physically or sexually abused; or fail to attend 3 consecutive therapy sessions without a reason judged by their therapist to be acceptable. For intent-to-treat purposes, all participants, including those who are terminated early, are followed at posttreatment and at 3 and 6 months.

*1.4.5. Therapist selection, training, and supervision*

At each of the 12 sites, 4 female therapists were randomly assigned to deliver either PE or PCT ($n=2$ per condition per site). Therapists were required to have either (a) an MD with specialization in psychiatry, or (b) a master's or doctoral degree in clinical or counseling psychology, social work, or psychiatric nursing. Prior experience treating PTSD in female veterans was required, but therapists were not required to have prior training in cognitive–behavioral techniques. Although it is not necessary for a therapist to be female in order to deliver PE or other trauma-focused treatment to female trauma survivors, only female therapists were included to minimize the likelihood that participants who had been sexually assaulted would find it difficult to discuss their trauma with a male therapist. This decision may limit the generalizability of findings but we adopted a cautious strategy because we used non-expert therapists.

By design, each therapist treats 10 participants: 2 training cases during a 6-month run-up period, and 8 randomized cases during 2 years of recruitment. In practice, therapists who attained sufficient proficiency were allowed to treat randomized cases after completing 1 training case and may treat more or fewer patients as required by circumstances, e.g., replacing a therapist who moves away during the study.

Two Therapy Training Centers, one for PE and one for PCT, coordinate the training and supervision of therapists. Each Training Center has a doctoral-level Master Therapist and 5–7 doctoral-level clinicians. At the beginning of the study, the Master Therapist and supervisory staff in each condition conducted an in-person group training for that condition. Therapists then receive supervision throughout their participation in the study. All therapy sessions are videotaped and are reviewed by the Training Center staff, who provide weekly individual supervision by telephone. The Training Center staff in each condition also conduct monthly group conference calls for all therapists in that condition to discuss study- and treatment-related issues. To optimize the rapid acquisition and maintenance of therapist skills, supervision is intensive, especially for the earliest cases. Supervision is titrated to skill level so that it becomes less intensive as therapists acquire more experience. All sessions are viewed and supervised weekly for

training cases and study cases 1–4. For study cases 5–8, all sessions are viewed and supervision is provided every other week.

*1.4.6. Fidelity monitoring*

A senior clinician who is independent of both PE and PCT treatment delivery will rate 10% of the videotapes using measures adapted from several randomized clinical trials of psychotherapy for PTSD [8,23,24]; the 10% figure was chosen arbitrarily in an attempt to ensure an adequate sample of information from each treatment condition. Because of the uniqueness and critical importance of therapist activities in Sessions 1 and 3 of PE, sessions were selected according to the following probabilities: 3/8 from Session 1, 3/8 from Session 3, and 2/8 from Sessions 2 and 4–10 combined. Although such reasons for selection do not apply to PCT, tapes are selected according to the same algorithm for purposes of comparability.

*1.5. Statistical methods*

The study was designed to enroll 8 participants for each of 4 therapists at the 12 participating sites. Participants are randomly assigned to PE or PCT using a permuted blocks design with varying block sizes. Sample size was computed on the basis of our primary hypothesis, that PE will be more effective than PCT for the treatment of PTSD due to military-related trauma in women as measured by the CAPS [11] at 3 months posttreatment. The 3-month CAPS score was used as the primary endpoint because data available during planning [7,25] indicated that the maximum benefit of PE was not observed immediately following treatment. Subsequent data from studies that employed a treatment protocol similar to the protocol used in CSP #494 indicate that the maximum benefit is observed at the end of treatment and is maintained over time [8,24].

Although treatment is delivered on an individual basis, each participant cannot be assumed to generate independent observations because participants are clustered within therapists. Thus, the computed sample size, based on the unpaired $t$-test statistic, was inflated by a factor, $f=1+(m-1)\rho$, to achieve the variance that one would have anticipated had there been no clustering [6,26–29]. The cluster size ($m$) is 8 (participants/therapist), and the intraclass correlation coefficient ($\rho$) was estimated from prior studies [8,25] to be in the range of .10 to .15, which in turn yields a sample size inflation factor of 1.7 to 2.05. With an estimated sample size of 384, this study has 85% to 90% statistical power to detect an effect of $d=.50$ at $\alpha=.05$, two-tailed.

The pivotal comparison will be the 3-month CAPS observation using a mixed effect model with treatment as a main effect and therapist as a random cluster effect nested within treatment. Immediate post-treatment and 6-month comparisons will also be made as secondary analyses, the latter to assess the durability of effects. Repeated measures analysis will also be performed on CAPS scores to determine the longitudinal effect of PE versus PCT. Effects of covariates such as additional treatment and the number of times participants have a brief visit with their non-study therapist will be examined by comparing groups on these variables. If groups differ, the covariate will be fitted and the treatment effect will be adjusted in the mixed model as secondary analysis. Cluster mean, linear interpolation, and multiple imputation will be used to impute missing data if necessary. If data are missing to the extent that imputation of missing values is inadvisable, hierarchical linear models [30] will be used. It is recognized, however, that the best approach to missing data is to minimize it [31].

Participants who did not adhere to the assigned strategy (i.e., fail to initiate treatment or complete 10 sessions) will be included in analyses as randomly assigned, according to the intention-to-treat principle [cf. [32]]. Formal interim analyses for efficacy are reported in an annual Data Safety and Monitoring Board meeting using the generalized group sequential method of Lan and DeMets [33] with the alpha-spending function that approximates the O'Brien–Fleming [34] sloped boundaries, which adjusts for multiple looks at the data while preserving a near nominal overall significance level.

## 2. Discussion

Multisite trials are an important stage in the process of evaluating an intervention. Linking together multiple sites facilitates the recruitment of large samples that yield high statistical power for both main analyses as well as secondary analyses of subgroups. Generalizability also is enhanced. Because data come from multiple sites, investigators can explore how a treatment's effects vary across sites and how such variation relates to site

characteristics. Multisite trials are expensive, however, so the decisions that must be made, such as which treatment or population to study, have particular significance. Below we discuss our rationale for making key decisions in the design of CSP #494.

### 2.1. Choice of treatment to study

A wide variety of drugs and psychotherapies are used for treating PTSD. The strongest evidence base is for selective serotonin reuptake inhibitors and cognitive–behavioral therapy (CBT). Both are recommended first-line treatments in evidence-based practice guidelines [35–37]. We focused on CBT because multisite trials of the selective serotonin reuptake inhibitors sertraline and paroxetine found that many PTSD patients failed to show clinically significant improvement, despite these drugs' overall effectiveness [38–41]. Single-site randomized clinical trials have consistently found that CBT produces marked improvements in PTSD symptoms and functioning [e.g., 7,8,24,25,42,43], but these trials typically have been done using expert therapists in a clinical research setting. Most clinicians, even those in VA PTSD programs, rarely use CBT [44,45]. Thus, it was important to determine how well CBT worked when delivered in a clinical setting by non-expert therapists. We addressed this question by employing VA and Department of Defense (DoD) therapists who varied in CBT skills.

There were several reasons why we chose to evaluate PE rather than another type of CBT. PE had the largest number of published studies at the time the study was planned [e.g., 7,8,39,46]. PE is effective when used by therapists who are not experts in CBT. Foa and colleagues (manuscript submitted for publication, 2005) have found effects with non-experts as therapists that are comparable to effects from studies with expert CBT therapists. PE can be used to treat a wide range of PTSD patients, including men and women, and military and non-military trauma survivors. PE appears to be equally effective for women who have and who have not experienced childhood sexual abuse [47,48], even though the former patients often have multiple comorbid problems and can be difficult to treat. Similar protocols for exposure therapy have been used to treat a wide range of other anxiety disorders, including panic disorder, specific phobia, and obsessive–compulsive disorder [cf. [49]]. Therapists who learn PE gain a versatile therapeutic tool for treating a number of clinical problems. We thought these generalizability and utility factors would facilitate the dissemination of PE if we found it to be effective.

Some might argue that a study such as ours, which incorporates effectiveness elements, should not require the use of a manual because therapy in clinical practice is seldom delivered using a manual. We decided to use a manual, however, because it is not unusual for a cognitive–behavioral treatment such as PE to be delivered according to a manual in a clinical setting. If a treatment is designed to be delivered according to a manual, then efforts should focus on facilitating manualized therapy as a routine practice.

### 2.2. Choice of a comparison treatment

Several considerations guided our choice of a comparison therapy. A design in which the comparison group received treatment was indicated because most of the evidence regarding the effects of PE came from studies that had used a wait-list (no treatment) control group. Although wait-list designs are useful for ruling out most threats to internal validity and establishing whether a treatment works, they yield no information about whether a specific treatment is better than the effects of treatment in general [50].

We rejected an augmentation design in which participants would be randomized to either care as usual, or care as usual plus PE. We also rejected a design in which participants would be randomized to either care as usual or PE. We used a manualized comparison condition to ensure internal validity given the lack of findings about the outcomes of care as usual in the treatment of female veterans and active duty personnel, along with the possibility that the behavior of therapists who delivered care as usual might change as a function of being in the study. Also to enhance internal validity, we used a nonspecific comparison design [50] in which the comparison treatment contained the nonspecific therapeutic factors generally present in usual care, such as therapist contact time and emotional support. PCT is characterized by nonspecific and supportive kinds of interventions, but does not include the trauma processing components of PE. Thus, if PE is more effective than PCT, we can infer that PE has benefits that are beyond those derived from therapy in general.

In addition, we felt that the comparison treatment had to be acceptable to both patients and therapists and had to address the concerns that many potential participants would present. PCT has a "here and now" focus on

current life difficulties that are directly or indirectly related to a trauma and aims to help patients consider ways to most constructively respond to these difficulties. It thus is clinically realistic in that it addresses the problems presented by many female veterans who seek PTSD care from the VA [12], which include medical problems (79%), interpersonal problems (59%), finances (46%), parenting issues (28%), and legal problems (25%).

### 2.3. Assignment of therapists to groups

One key decision faced by psychotherapy researchers is how to assign therapists to treatments in order to minimize therapist effects. Schnurr et al. [6] discussed various strategies: using experts in a given treatment to deliver that treatment only; assigning therapists to deliver both treatments; and randomly assigning therapists to the treatment that they deliver. The former strategy was irrelevant given our aim of ensuring that non-experts could deliver the treatment under study. Of the remaining two alternatives, we chose to have each therapist deliver only one treatment because the use of a therapist to deliver both treatments does not control for such effects as skill in delivering particular treatments, enthusiasm, preference for a particular approach, and other potential sources of bias. We were additionally concerned that having therapists deliver both treatments would make it difficult for them to keep the treatments distinct in application. These potential risks may be necessary in single-site trials in which there are few therapists. In such circumstances, it is essential that treatments are delivered with equivalent skill, warmth, and other similar factors and that therapist behavior is rigorously monitored to detect any differences that occur.

In CSP #494, the multisite format permitted us to control for therapist effects by randomly assigning a large number of therapists to treatment conditions. Experience with this strategy in CSP #420 [6,23] was positive. There were no problems with therapists wanting to switch their assignments, or in adhering to their assigned therapy if it was not their preferred therapy. After participating, only 4% of therapists said that they preferred the therapy to which they had not been assigned, 88% preferred their assigned therapy (85% trauma-focused and 92% present-centered), and 8% had no preference.

Experience with this strategy in CSP #494 has generally been positive, although some therapists who were assigned to PCT initially expressed concerns about delivering a “lesser” therapy. An unanticipated complication of using separate therapists to deliver each individual therapy, however, is that a patient cannot be randomized unless a therapist in each condition is available to treat another patient. Our therapists are VA and DoD clinicians who see many patients in addition to those who are enrolled in the CSP #494. On occasion, randomization of eligible patients at a site had to be delayed until a therapist in each condition was able to accept a new patient. Investigators in future multisite psychotherapy trials should ensure that there is sufficient treatment capacity so that such delays are prevented.

### 2.4. Supervision and fidelity monitoring

Psychotherapy research requires quality control procedures to be incorporated in a study’s design. Supervision is used in an attempt to ensure delivery of treatments as specified by the protocol. Monitoring is used to check whether this in fact has occurred, i.e., that therapists are delivering the interventions specified in the manual and not using interventions that are proscribed. In CSP #494, the first objective is particularly important for the PE condition, and the second is particularly important for the PCT condition. Monitoring is also used to assess therapist competence. The adherence and competence ratings are independent of the supervision process to facilitate comparisons between treatments and also between sites.

As in CSP #420 [6], quality control procedures in CSP #494 include detailed treatment manuals for both active and comparison treatments, formal training procedures for therapists, videotapes of all therapy sessions, and use of these tapes for ongoing telephone supervision of therapists and adherence and fidelity monitoring. In a multisite format, these tasks need to be achieved across long distances and thus require the equipment necessary for making and copying videotapes or DVDs, computers, phones, etc. and the administrative structure necessary to ensure that tapes get copied and mailed and that individual and group supervision occur as planned.

### 2.5. Efficacy versus effectiveness considerations

By the time a treatment is studied in a multisite format, there usually are a number of smaller studies that provide strong evidence of the treatment’s benefits. It is not uncommon for these studies to have used tightly controlled

efficacy designs [for further discussion, see Ref. [51]], which makes sense as a way of enhancing statistical power with a small sample. For example, therapists in psychotherapy studies may be experts in the technique under investigation. Patients may be excluded for significant psychiatric comorbidity, and only data from patients who complete the treatment may be included in analysis. These studies may have high internal validity but their results may not generalize to real-world clinical settings. Effectiveness studies, which are less tightly controlled, are more generalizable but may have unacceptably low validity.

Given the strength of evidence from single-site trials of PE, we felt that a multisite efficacy study was not necessary. Instead, we reasoned that the advantages of the multisite format should be employed to address the question of how well PE would work in clinical practice. Thus, the design of CSP #494 reflects a commitment to optimally combine efficacy and effectiveness methods, as recommended by Seligman [51]. The study is a randomized clinical trial with features designed to maintain internal and construct validity while enhancing clinical realism and generalizability: inclusion of participants who have comorbid problems; use of non-expert therapists; implementation of the protocol at several settings (VA mental health programs, VA Vet Centers, and a DoD mental health program); allowance of multiple types of co-therapy during active study treatment; and measurement of multiple outcome domains.

Our aim is to provide scientifically useful information to the field at large while helping the VA shape policy and practice. Accordingly, we will perform intention-to-treat analysis, in which data from each randomized patient are used regardless of the patient's compliance or quality of treatment. As noted by Lachin [31], intention-to-treat is the recommended standard for treatment research, e.g., by the Food and Drug Administration and the National Institutes of Health [52]. This approach to analysis addresses a pragmatic question: "Is it better to adopt a policy of Treatment A if possible, with deviations if necessary, or a policy of Treatment B, if necessary, for patients who seem to have this disease" [32, p. 29]. Our results can provide reasonable confidence about the impact on the system if PE is widely adopted.

## 3. Closing comments

CSP #494 was designed with several goals in mind. One is to expand knowledge about the treatment of PTSD in military women. There have been no prior trials of PTSD treatment for female veterans or active duty personnel. Another goal is to expand knowledge about the treatment of PTSD. Except for CSP #420, there have been no other comparably large, multi-site trials of psychotherapy for PTSD. The large sample and multi-site format will yield high statistical power and provide evidence of the effectiveness of Prolonged Exposure compared with a more usual and customary type of care.

Cognitive–behavioral techniques are not widely used for the treatment of PTSD [44,45], even though they are recommended by PTSD practice guidelines [35–37]. Thus, a third goal is to facilitate the dissemination of evidence-based treatment. Generalizability of our findings is enhanced by the incorporation of effectiveness elements and because treatment is delivered by a broad cross-section of VA and DoD therapists within the same settings where many female active duty and veteran women receive their health care. If PE is found to be effective, the manual and training procedures used in this study can assist VA and DoD in providing quality care to women who have PTSD.

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